Good Naming, Labeling, and Packaging Practices to Reduce Medication Errors:

Carton Labeling and Container Label

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Background

- 33% of medication errors reported to the ISMP Reporting Program may be attributed to the packaging and labeling of drug products, including 30% of fatal errors.
- IOM has requested that FDA develop and enforce standards for the design of drug packaging and labeling that will maximize safety in use.
- To help reduce errors, DMEPA assesses the labels and labeling:
  - using the principles of Human Factors Engineering (HFE)
  - Failure Mode and Effects Analysis (FMEA)
  - Lessons learned from post-marketing experience

Carton Labeling and Container labels

Common Sources of Error

- Inadequate differentiation between different drugs or strengths
- Confusing statements
- Missing/excessive information
- Distracting images
- Small font size/illegible information
- Error-prone abbreviations or symbols
- Expression of strength, established name, dosage form

Typical Pharmacy Shelf

CDER Evaluation

- Drug manufacturers submit carton labeling and container labels to CDER electronically or hard copies
- CDER evaluates most carton labeling and container labels prior to approval or marketing
  - NDA, BLA, and ANDA products
    - Prescription and Over-the-Counter (OTC)
- Multidisciplinary evaluation

Carton Labeling and Container Labels

- CDER provides recommendations to drug manufactures that aim to reduce errors
  - Effectiveness of interventions unknown
- Regulations provide some direction:
  - Type of information
  - Placement of information
  - Prominence/size of information
  - Barcodes
- Currently, no CDER Guidance for Industry describing design aspects
- Input from this meeting will be used to develop GNLP guidance

Panel 1: Questions

1. What does CDER need to consider to ensure that the container labels and carton labeling designs are safe and reduce the risk of medication errors?
2. What are the challenges in designing container labels and carton labeling to reduce the risk of medication errors?
3. What are some strategies for addressing these design challenges without compromising safety?

Good Naming, Labeling, and Packaging Practices to Reduce Medication Errors: **Studies to Evaluate Carton Labeling and Container Labels**

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Background

- Human Factors studies, Failure Modes and Effects Analyses (FMEAs), and other types of proactive risk assessments may be used to identify error-prone aspects of carton and container label designs
- Not required by Regulation
- No guidance provided currently for drug products
  - CDRH has HF guidance for medical devices

Current Practices

- Studies are voluntary and may be:
  - Requested by CDER
  - Self-initiated by the drug manufacturer
- CDER may or may not see protocol prior to study initiation
- Studies may focus on the label design for a single product, comparing two different products, or across an entire manufacturers product line
- Results are provided in summary reports to CDER when label designs are submitted
- CDER considers the results in our evaluation of the carton labeling and container labels

Review Considerations

- Studies vary in design: endpoints, study population/size, setting, methodology, data collection, etc.
- Study may have methodological limitations
- Data submissions to CDER may be incomplete or hard to follow
- Data captured may be ambiguous
- Unclear what endpoints are appropriate measures of success to reduce medication errors
- Unclear if results of one study are relevant to container/carton design of other drug products not included in the study

Panel 2: Questions

1. What are the strengths and limitations of performing such studies?
2. Are there other types of studies and analyses that provide useful information about the medication error risks associated with the container label or carton labeling design?
3. How can CDER ensure that the study design accurately captures and assesses potential medication error risks that should be considered in our evaluation of the container labels and carton labeling?

Good Naming, Labeling, and Packaging Practices to Reduce Medication Errors: **Studies to Evaluate Packaging**

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June 24, 2010

Background

- 33% of medication errors reported to the ISMP Reporting Program may be attributed to the packaging and labeling of drug products, including 30% of fatal errors
- IOM has requested that FDA develop and enforce standards for the design of drug packaging and labeling that will maximize safety in use
- To help reduce errors, DMEPA evaluates drug packaging intended for commercial distribution using
  - Principles of Human Factors Engineering (HFE)
  - Failure Mode and Effects Analysis (FMEA)
  - Lessons learned from post-marketing experience

Commercial Drug Packaging

Common Sources of Error

- Packaging a drug product in a container/closure system that implies or affords a route of administration other than intended. For example,
  - Oral drug products packaged in injectable vial containers
  - Oral inhalation products packaged in capsules
  - Topical products packaged with closures that look similar to nasal, eye, or ear products
- Providing an amount of drug in a commercial container that is incongruent with recommended doses
  - Vial overfill
  - Excess drug in transdermal patches
  - Multiple units required to achieve usual dose

Commercial Drug Packaging

Common Sources of Error

- Configuration of solid oral dosage forms in blister packaging
  - Presentation and sequencing of doses: using a fixed-dose configuration for a variable dosage regimen, grouping of tablets, etc
- Drug-device combination products (such as inhalers, prefilled pens)
  - Unusual/unexpected device operation
  - Lack of protection against incorrect use
  - Confusing or complex controls, labeling, operation
  - Defeatable or ignorable safety features

CDER Evaluation

- Drug manufacturers submit descriptions of drug packaging to CDER electronically or hard copies
- Some drug manufacturers provide actual samples of the drug packaging design
- Studies assessing risk associated with drug packaging not required
- CDER evaluates the drug packaging design prior to approval or marketing
  - IND, NDA, BLA, and ANDA products
    - Prescription and Over-the-Counter (OTC)
- Multidisciplinary evaluation

Packaging Studies: Current Practices

- Studies are voluntary and may be:
  - Requested by CDER
  - Self-initiated by the drug manufacturer
- CDER may or may not be consulted by the firm to comment on a protocol prior to study initiation
- Studies may focus on the packaging design design for a single product, or comparing two different packaging designs (for the same or different products)
- Results are provided in summary reports to CDER
- CDER considers the results in our evaluation of the packaging and associated labeling

Review Considerations

- Studies vary in design: endpoints, study population/size, setting, methodology, data collection, etc.
- Study may have methodological limitations
- Data submissions to CDER may be incomplete or hard to follow
- Data captured may be ambiguous
- Unclear what endpoints are appropriate measures of success to reduce medication errors
- Unclear if results of one study are relevant to the packaging design of other drug products not included in the study

Drug Packaging Design

- CDER provides recommendations to drug manufactures that aim to reduce errors
  - Effectiveness of interventions often is unknown
- Regulations provide some guidance, particularly from a chemistry perspective
- Currently, no CDER Guidance for Industry describing packaging design aspects and evaluation techniques from a medication errors perspective
  - Principles outlined in CDRH's HF guidance for medical devices somewhat applicable
- Input from this meeting will be used to develop GNLP guidance

Manufacturing Considerations

- Depending on timing and other drug-dependent issues, manufacturers may have limited ability to affect substantial packaging changes
  - In some cases, labeling and educational measures proposed as alternative strategies to manage a medication error risk related to packaging

Panel 3: Questions

1. What information does CDER need to consider to ensure that the manufacturers' packaging design is safe and reduces the risk for medication errors?
2. What are the challenges in designing manufacturers' packaging to reduce the risk of medication errors?
3. What are some strategies for addressing these challenges without compromising safety?
4. How can CDER ensure that the study design accurately captures and assesses potential medication error risks that should be considered in our evaluation of a proposed manufacturers' packaging design for a particular medication?
5. Are there other types of studies and analyses that provide useful information about the medication error risks associated with the manufacturers' packaging design?

Good Naming, Labeling, and Packaging Practices to Reduce Medication Errors: **Proprietary Name Development**

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Background

- Drug names are a critical “identifier” of products
- Drug name confusion or identification failures lead to error
  - Confusion related to product names is one of the most common causes of errors reported to ISMP and CDER
- The Institute for Safe Medication Practices (ISMP) Institute of Medicine (IOM), World Health Organization (WHO), and the Joint Commission have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval

Proprietary Names

Common Sources of Error

- Look-alike/sound-alike names
  - Similar to other proprietary/established names
  - Including USAN stems and mimic established names
- Modifier omission or oversight
- Failure to recognize active ingredient (Dual Proprietary Names, Brand Name Line Extension, Umbrella branding)
- Encoding numerals
- Dangerous abbreviations and medical abbreviations
- Length of names: number of letters, multiword names

Categories of Proprietary Names

- Novel proprietary name
  - Root name only
  - Proprietary name with a modifier
  - Dual Proprietary Names
- Brand Name Line Extension
  - Marketed proprietary name with a modifier
  - Umbrella branding

Definition of a Modifier

- Letters, words, numbers or combination thereof added to the beginning or end of a proprietary name
- May have a function, such as to:
  - Identify a modified dosage formulation
  - Differentiate the dosing schedule
  - Designate product strength
  - Identify active ingredient

Placement of Modifiers

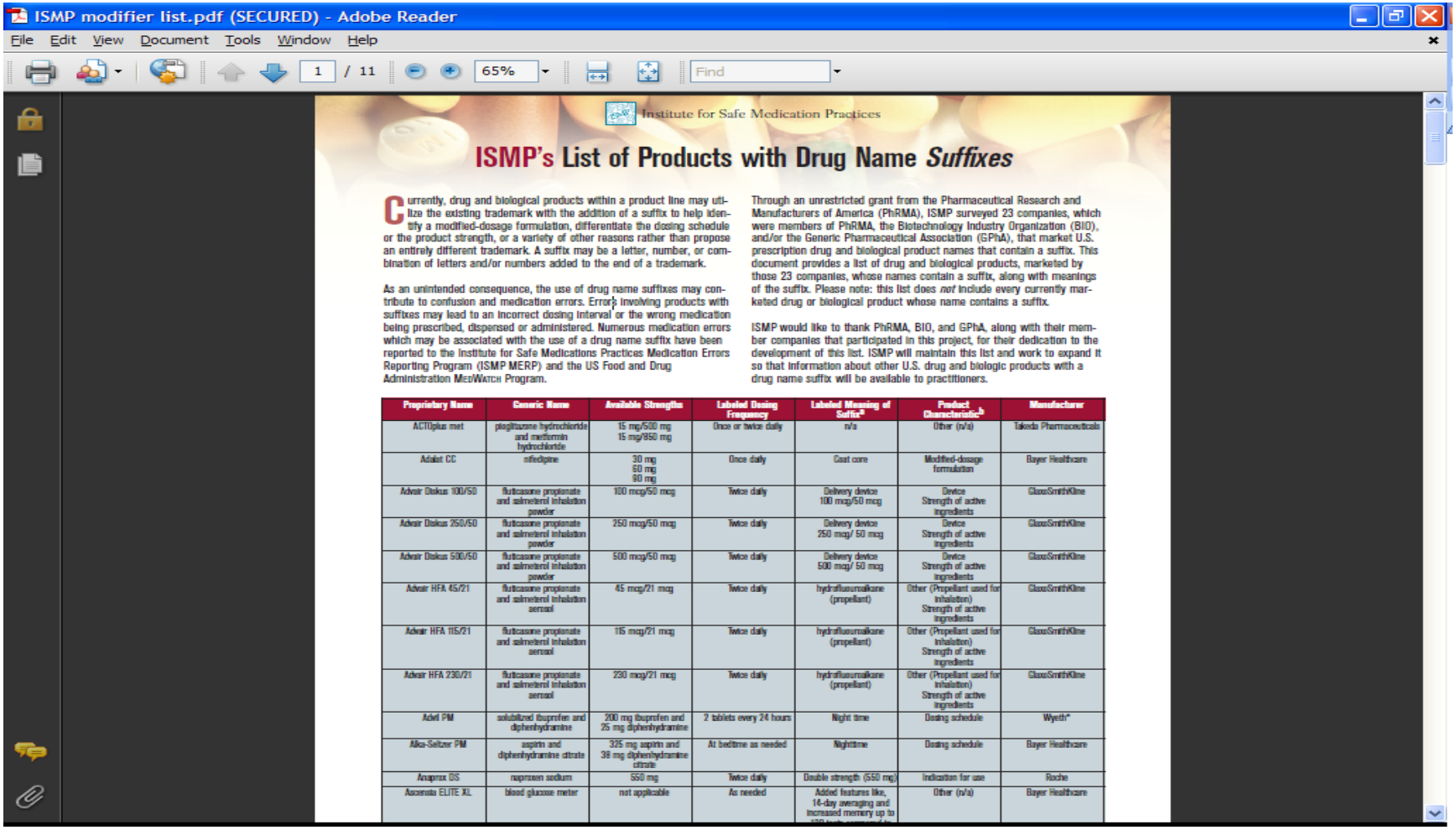
- Beginning of name
  - Lo Seasonique
  - sfRowasa
  - Tri-Luma
- Middle of name
  - Ortho Tri-Cyclen
- End of name
  - Asacol HD
  - Toprol XL
  - Zofran ODT
  - Plan B One-Step
- Combination
  - Low-Ogestrel-28

Institute of Medicine 2006 Report Recommendation

- Recommendation 4:
  - "The FDA and industry should collaborate to develop (1) a common drug nomenclature that standardizes abbreviations, acronyms, and terms, to the extent possible.."[1]

1. Preventing Medication Errors: Quality Chasm Series, July 2006, Page 274.

ISMP List of Products with Drug Name Suffixes 2010



ISMP modifier list.pdf (SECURED) - Adobe Reader

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Institute for Safe Medication Practices

ISMP's List of Products with Drug Name *Suffixes*

Currently, drug and biological products within a product line may utilize the existing trademark with the addition of a suffix to help identify a modified-dosage formulation, differentiate the dosing schedule or the product strength, or a variety of other reasons rather than propose an entirely different trademark. A suffix may be a letter, number, or combination of letters and/or numbers added to the end of a trademark.

As an unintended consequence, the use of drug name suffixes may contribute to confusion and medication errors. Errors involving products with suffixes may lead to an incorrect dosing interval or the wrong medication being prescribed, dispensed or administered. Numerous medication errors which may be associated with the use of a drug name suffix have been reported to the Institute for Safe Medications Practices Medication Errors Reporting Program (ISMP MERP) and the US Food and Drug Administration MedWatch Program.

Through an unrestricted grant from the Pharmaceutical Research and Manufacturers of America (PhRMA), ISMP surveyed 23 companies, which were members of PhRMA, the Biotechnology Industry Organization (BIO), and/or the Generic Pharmaceutical Association (GPhA), that market U.S. prescription drug and biological product names that contain a suffix. This document provides a list of drug and biological products, marketed by those 23 companies, whose names contain a suffix, along with meanings of the suffix. Please note: this list does *not* include every currently marketed drug or biological product whose name contains a suffix.

ISMP would like to thank PhRMA, BIO, and GPhA, along with their member companies that participated in this project, for their dedication to the development of this list. ISMP will maintain this list and work to expand it so that information about other U.S. drug and biologic products with a drug name suffix will be available to practitioners.

Proprietary Name	Generic Name	Available Strengths	Labeled Dosing Frequency	Labeled Meaning of Suffix[a]	Product Characteristic[b]	Manufacturer
ACTOplus met	pioglitazone hydrochloride and metformin hydrochloride	15 mg/500 mg 15 mg/850 mg	Once or twice daily	n/a	Other (n/a)	Takeda Pharmaceuticals
Adalat CC	nifedipine	30 mg 60 mg 90 mg	Once daily	Coat core	Modified-dosage formulation	Bayer Healthcare
Advair Diskus 100/50	fluticasone propionate and salmeterol inhalation powder	100 mcg/50 mcg	Twice daily	Delivery device 100 mcg/50 mcg	Device Strength of active ingredients	GlaxoSmithKline
Advair Diskus 250/50	fluticasone propionate and salmeterol inhalation powder	250 mcg/50 mcg	Twice daily	Delivery device 250 mcg/ 50 mcg	Device Strength of active ingredients	GlaxoSmithKline
Advair Diskus 500/50	fluticasone propionate and salmeterol inhalation powder	500 mcg/50 mcg	Twice daily	Delivery device 500 mcg/ 50 mcg	Device Strength of active ingredients	GlaxoSmithKline
Advair HFA 45/21	fluticasone propionate and salmeterol inhalation aerosol	45 mcg/21 mcg	Twice daily	hydrofluoroalkane (propellant)	Other (Propellant used for inhalation) Strength of active ingredients	GlaxoSmithKline
Advair HFA 115/21	fluticasone propionate and salmeterol inhalation aerosol	115 mcg/21 mcg	Twice daily	hydrofluoroalkane (propellant)	Other (Propellant used for inhalation) Strength of active ingredients	GlaxoSmithKline
Advair HFA 230/21	fluticasone propionate and salmeterol inhalation aerosol	230 mcg/21 mcg	Twice daily	hydrofluoroalkane (propellant)	Other (Propellant used for inhalation) Strength of active ingredients	GlaxoSmithKline
Advil PM	solubilized ibuprofen and diphenhydramine	200 mg ibuprofen and 25 mg diphenhydramine	2 tablets every 24 hours	Night time	Dosing schedule	Wyeth*
Alka-Seltzer PM	aspirin and diphenhydramine citrate	325 mg aspirin and 38 mg diphenhydramine citrate	At bedtime as needed	Nighttime	Dosing schedule	Bayer Healthcare
Anaprox DS	naproxen sodium	550 mg	Twice daily	Double strength (550 mg)	Indication for use	Roche
Ascensia ELITE XL	blood glucose meter	not applicable	As needed	Added features like, 14-day averaging and increased memory up to	Other (n/a)	Bayer Healthcare

Modifiers May Lead to Errors

- Risk of modifier being omitted during prescribing or overlooked in dispensing/administration leading to confusion with currently marketed root name product
  - Even if the modifier is suitable, the modifier can still be dropped. What is the impact of the dropped modifier?
- Risk of modifier being misinterpreted (e.g. as frequency, strength, route of administration, other drug products)
- Risk of misunderstanding of modifier meaning
  - For example, healthcare providers or patients might interpret ‘EC’ to mean that you can take a product without food when in fact a product can be given with or without food

Current CDER Considerations when Evaluating a Modifier

- Does the root name exist as a currently marketed product?
- Has the applicant provided a rationale for the modifier? (i.e. XR to differentiate the extended-release product from an immediate release formulation)
- Is the placement of the modifier be appropriate? (i.e. before root name versus after the name)
- Has the applicant provided the intended definition for the modifier? (e.g. ER is meant to indicate extended-release)
- Does the modifier currently exist and if so, does the intended meaning reflect the current usage?
- If the modifier describes a dosage form, does the proposed modifier align with the official dosage form designation or definition?
- Can the intended meaning be communicated by another modifier? (i.e. XR and ER both have been used to convey extended-release)
- If a modifier is not used in the proprietary name, are there additional safety concerns with using the root name or a different proprietary name?

Definition of Dual Proprietary Name

- A different proprietary name for the same active ingredient marketed by the same manufacturer
- Proposed product may introduce new or different product characteristics than the original product (e.g. indication, dosage form, frequency of administration, dose)

Safety Risk Associated with Dual Proprietary Names

- Concomitant therapy
  - Patients and practitioners not aware the two products contain the same active ingredient and use products concomitantly
- Drug-drug interaction
  - Patients and practitioners not aware that a particular product contains an active ingredient and uses a product unknowingly leading to a drug interaction
    - For example, nitroglycerin used to treat a patient on Revatio (sildenafil) because the drug-drug interaction is not recognized

Brand Name Line Extenstion (BNLE)

- Brand Name Line Extension (BNLE): Use of a root name across a product line

  -**Claritin, Claritin-**D 24-Hour, Children's **Claritin** Grape Chewables

  -**Zyrtec**, **Zyrtec**-D, Children's **Zyrtec** Allergy Syrup
- Long-standing practice with OTC products
- BNLE products currently marketed as monograph, NDA, and ANDA products

BNLE: Umbrella Branding

- Products with the same root name generally share at least one active ingredient
  - **Claritin** (loratadine), **Claritin-**D 24-Hour (loratadine/pseudoephedrine), Children's **Claritin** Grape Chewables (loratadine)
  - **Zyrtec** (cetirizine), **Zyrtec**-D (cetirizine/pseudoephedrine), Children's **Zyrtec** Allergy Syrup (cetirizine)
- Umbrella branding: when the same root name is used for products that do NOT share any active ingredients with the base brand
  - **Claritin** Eye (ketotifen fumarate)
  - **Zyrtec** Itchy Eye (ketotifen fumarate)

Medication Errors Reported with BNLE/Umbrella Branding

- Types of errors
  - Use of wrong product
  - Administration of unnecessary active ingredient
  - Wrong indication
  - Wrong patient population
- Likelihood of error and risk of harm may be increased when a name is used for products that do not share at least one active ingredient

BNLE and Umbrella Branding from a Regulatory Perspective

- No regulation explicitly prohibits
- No guidance outlines appropriate use of proprietary names

CDER Name Evaluation

- Generally, proprietary names evaluated by CDER prior to marketing
  - IND, NDA, BLA, ANDA
    - Prescription and Over-the-Counter (OTC)
- Established names designated by the U.S. Adopted Names (USAN) Council
- Occasionally, drug manufacturers seek CDER advice on proprietary nomenclature options
  - Product line extensions
  - After primary proposed proprietary name found unacceptable

CDER Proprietary Name Evaluation Considerations

- Promotional
  - Led by Division of Drug Marketing, Advertising, and Communications (DDMAC)
  - Avoid names that are overly fanciful, overstate product efficacy, minimize risk, broaden product indications, or make unsubstantiated superiority claims.
- **Safety**
  - **Led by Division of Medication Error Prevention and Analysis (DMEPA)**
  - **Avoid error-prone names**
- Regulatory
  - Comply with Regulatory requirements set forth by CFR

Nomenclature Studies: Current Practices

- Studies are voluntary and may be:
  - Suggested by CDER
  - Self-initiated by the drug manufacturer
- CDER may or may not be consulted by the firm to comment on a protocol prior to study initiation
- Results are sometimes provided in reports to CDER when proprietary names are submitted

Nomenclature studies: Current Practices

- Focus of studies varies:
  - Look and sound-alike evaluations
  - Study of modifier to show consistent meaning in clinical setting (i.e. XR understood as extended-release)
  - Study of modifier to compare risks of Root Name plus Modifier versus New Proprietary Name
  - Label comprehension to assess consumer and HCP ability to differentiate between base brand product and BNLE or proposed modifier product.
- Data is considered by DMEPA in proprietary name evaluation

Review Considerations

- Studies vary in design: endpoints, study population/size, setting, methodology, data collection, etc.
- Study may have methodological limitations
- Data submissions to CDER may be incomplete or hard to follow
- Data captured may be ambiguous
- Unclear what endpoints are appropriate measures of success to reduce medication errors
- Unclear if results of one study can be used to inform nomenclature of other drug products not included in the study

Proprietary Names: CDER role in approval

- CDER finds names acceptable/unacceptable based on promotional, safety, and regulatory considerations
  - DMEPA issues decisional letters
- Utility of mitigation strategies is unclear when proprietary name safety issues are identified pre-marketing
- Specific regulations apply to proprietary names
- Limited guidance from CDER describing appropriate aspects to consider from a medication errors perspective
  - Concept Paper outlines some testing methodology
  - Complete Submission guidance outlines elements required for FDA review
- Input from this meeting will be used to develop GNLP guidance

Panel 4: Questions

1. What are the challenges in developing a proprietary name to reduce medication errors?
2. What are some strategies for addressing these challenges without compromising safety?
3. When products are developed containing the same ingredient as a marketed product, how can risks associated with a given nomenclature strategy (i.e. use of a modifier "*Proprietary Name* ER" versus the use of an alternate proprietary name) for a proposed product be evaluated, assessed, and mitigated?
4. When applicants wish to use the same proprietary name for products containing different ingredient(s), how can risks associated with this practice evaluated, assessed, and mitigated?